66, 145, 166, 177, 191, 202. 212, and 227, Figure 2) which are structurally important and involved in the formation of 5 disulfide bonds. The similar hydrophobicity plots of HPAK and GI 186653 (Figures 3 and 4) support the premise that these molecules have a similar structure. Applicants' invention is described in detail throughout the specification of the above identified application.

Utility rejections under 35 U.S.C. § 101 and § 112

Claims 1 and 18-20 stand rejected under 35 U.S.C. § 101 and § 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that, "the claimed invention is not supported by either a specific asserted utility or a well-established utility." The rejections of claims 1 and 18-20 are improper, as the claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue is a polypeptide sequence corresponding to a gene that is expressed in humans, including human tumors. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which necessarily require detailed knowledge of how the polypeptide works. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Any of these uses meets the utility requirements of 35 U.S.C. § 101 and, derivatively, § 112, first paragraph. Under these sections of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999). In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991) the United States Court of Appeal

for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464; *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case the Patent Office bears the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The rejection fails to demonstrate either that the Applicants' assertions of utility are legally insufficient or that a person of ordinary skill in the art would reasonably doubt that they could be achieved. For these reasons alone the rejections should be withdrawn.

There is, however, an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law. These inconsistencies are discussed separately below.

I. Use of the claimed polypeptides for diagnosis of conditions or diseases characterized by expression of HPAK, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There is a "well-established" use for the claimed invention, there are specific practical and beneficial uses for the invention, and those uses are substantial. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of human polynucleotides and their encoded polypeptides as tools for toxicology testing, drug discovery, and the diagnosis of disease is "well-established"

In recent years, scientists have developed important techniques for toxicology testing, drug development, and disease diagnosis. Many of these techniques rely on expression profiling, in which the expression of numerous genes is compared in two or more samples. Genes or gene fragments known to be expressed, such as the invention at issue, are tools essential to any technology that uses expression profiling. Likewise, proteome expression profiling techniques have been developed in which the expression of numerous polypeptides is compared in two or more samples. Polypeptide or polypeptide fragments known to be expressed are tools essential to any technology that uses proteome expression profiling. See, *e.g.*, Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467 (2000).

The technologies made possible by expression profiling and the DNA and polypeptide tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. One of these techniques is toxicology testing, used in both drug development and safety assessment. Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29(7):655, 656 (1999):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the

> developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153 (1999); Sandra Steiner and N. Leigh Anderson, *supra.*

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> ... for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107(8):681 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening. This is true for both polynucleotides and polypeptides encoded by them.

There are numerous additional uses for the information made possible by expression profiling. Expression profiling is used to identify drug targets and characterize disease. See Rockett et al., *supra.* It also is used in tissue profiling, developmental biology, disease staging, etc. There is simply no doubt that the sequences of expressed human genes all have practical,

substantial and credible real-world utilities, at the very least for expression profiling.

Expression profiling technology is also used to identify drug targets and analyze disease at the molecular level, thus accelerating the drug development process. For example, expression profiling is useful for the elucidation of biochemical pathways, each pathway comprising a multitude of component polypeptides and thus providing a pool of potential drug targets. In this manner, expression profiling leads to the optimization of drug target identification and a comprehensive understanding of disease etiology and progression.

There is simply no doubt that the sequences of expressed human polynucleotides and polypeptides all have practical, substantial and credible real-world utilities, at the very least for biochemical pathway elucidation, drug target identification, and assessment of toxicity and treatment efficacy in the drug development process. Sandra Steiner and N. Leigh Anderson, *supra*, have elaborated on this topic as follows:

> The rapid progress in genomics and proteomics technologies creates a unique opportunity to dramatically improve the predictive power of safety assessment and to accelerate the drug development process. Application of gene and protein expression profiling promises to improve lead selection, resulting in the development of drug candidates with higher efficacy and lower toxicity. The identification of biologically relevant surrogate markers correlated with treatment efficacy and safety bears a great potential to optimize the monitoring of pre-clinical and clinical trials.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

B. The use of HPAK for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

Even if, *arguendo*, toxicology testing, drug development and disease diagnosis (through expression profiling) are not well-established utilities (which expressly is not conceded), the claimed invention nonetheless has specific utility by virtue of its use in each of these techniques. There is no dispute that the claimed invention is in fact a useful tool in each of these techniques. That is sufficient to establish utility for both the polypeptide and the polynucleotides encoding it.

Nevertheless, the claimed invention is rejected on the grounds that it does not have a "specific utility" absent a detailed description of the actual function of the claimed protein or identification of a "specific" disease it can be used to treat. Apparently relying on the Training Materials, the rejection is made based on a scientifically incorrect and legally unsupportable assertion that identification of the family or families of proteins to which the claimed invention belongs, without more, does not satisfy the utility requirement. None of these grounds is consistent with the law.

1. A patent applicant can specify a utility without any knowledge as to how or why the invention has that utility

It is settled law that how or why any invention works is irrelevant to determining utility under 35 U.S.C. § 101: "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortright*, 165 F.3d, at 1359 (quoting *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340 (Fed. Cir. 1989)). *See also Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the

practical effectiveness of his invention rests."). It follows that the patent applicant need not set forth the particular functionality of the claimed invention to satisfy the utility requirement.

Practical, beneficial use, not functionality, is at the core of the utility requirement. *Supra* (introduction to § I). So long as the practical benefits are apparent from the invention without speculation, the requirement is satisfied. *Standard Oil* Co. v. *Montedison*, 664 F.2d 356, 374, 212 USPQ 327 (3d Cir. 1981); *see also Brana*, 51 F.3d at 1565. To state that a biological molecule might be useful to treat some unspecified disease is not, therefore a specific utility. *In re Kirk*, 376 F.2d 936, 945, 153 USPQ 48 (C.C.P.A. 1967). The molecule might be effective, and it might not.

However, unlike the synthetic molecules of *Kirk*, the claimed invention is **known** to be useful. It is not just a random sequence of speculative use. Because it is expressed in humans, a person of ordinary skill in the art would know how to use the claimed polypeptide sequences -- without any guesswork -- in toxicology testing, drug development, and disease diagnosis regardless of how the polypeptide actually functions. The claimed invention could be used, for example, in a toxicology test to determine whether a drug or toxin causes any change in the expression of kallikreins. Similarly, the claimed invention could be used to determine whether a specific medical condition, such as cancer, affects the expression of kallikreins and, perhaps in conjunction with other information, serve as a marker for or to assess the stage of a particular disease or condition.

In fact, the claimed polypeptide sequences could be used in toxicology testing and diagnosis without **any** knowledge (although this is not the case here) of the protein for which it codes: it could serve, for example, as a marker of a toxic response, or, alternatively, if levels of the claimed polypeptides remain unchanged during a toxic response, as a control in toxicology testing. Diagnosis of disease (or fingerprinting using expression profiles) can be achieved using arrays of numerous identifiable, expressed DNA sequences, or by two-dimensional gel analysis of the expressed proteins themselves, notwithstanding lack of any knowledge of the specific functions of the proteins they encode.

2. A patent applicant may specify a utility that applies to a broad class of inventions

The fact that the claimed invention is a member of a broad class (such as DNA sequences

or the proteins they encode expressed in humans) that includes sequences other than those claimed that also have utilities in toxicology testing, drug discovery, disease diagnosis, etc. does not negate utility. Practical utilities can be directed to classes of inventions, irrespective of function, so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. *Montedison*, 664 F.2d at 374-75. The law has long assumed that inventions that achieve a practical use also achieved by other inventions satisfy the utility requirement. For example, many materials conduct electricity. Likewise, many different plastics can be used to form useful films. *Montedison*, 664 F.2d at 374-75; *Natta*, 480 F.2d at 1397. This is a general utility (practical films) that applies to a broad class of inventions (plastics) which satisfies the utility requirement of 35 U.S.C. § 101.

Not all broad classes of inventions are, by themselves, sufficient to inform a person of ordinary skill in the art of the practical utility for a member of the class. Some classes may indeed convey too little information to a person of ordinary skill in the art. These may include classes of inventions that include both useful and nonuseful members. *See In re Ziegler*, 992 F.2d 1197, 1201, 26 USPQ2d 1600 (Fed. Cir. 1993). In some of these cases, further experimentation would be required to determine whether or not a member of the class actually has a practical use. *Brenner*, 383 U.S. at 534-35.

The broad class of steroids identified in *Kirk* is just such a class. It includes natural steroids (concededly useful) and man-made steroids, some of which are useful and some of which are not. Indeed, only a small fraction of the members of this broad class of invention may be useful. Without additional information or further experimentation, a person of ordinary skill in the art would not know whether a member of the class falls into the useful category or not. This could also be the case for the broad class of "plastic-like" polypropylenes in *Ziegler*, which includes many -- perhaps predominately -- useless members.

The PTO routinely issues patents whose utility is based solely on the claimed inventions' membership in a class of useful things. The PTO presumably would issue a patent on a novel and nonobvious fishing rod notwithstanding the lack of any disclosure of the particular fish it might be used to catch. The standard being promulgated in the Guidelines and in particular as exemplified in the Training Materials, and being applied in the present rejection, would appear to warrant a rejection, however, on the grounds that the use of the fishing rod is applicable to the

general class of devices used to catch fish.

The PTO must apply the same standard to the biotechnological arts that it applies to fields such as plastics and fishing equipment. *In re Gazave*, 379 F.2d 973, 977-78, 154 USPQ 92 (CCPA 1967) *quoting In re Chilowsky*, 299 F.2d 457, 461, 108 USPQ 321 (CCPA 1956) ("[T]he same principles should apply in determining operativeness and sufficiency of disclosure in applications relating to nuclear fission art as in other cases."); *see also In re Alappat*, 33 F.3d 1526, 1566, 31 USPQ2d 1545 (Fed. Cir. 1994) (Archer, C.J., concurring in part and dissenting in part) ("Discoveries and inventions in the field of digital electronics are analyzed according to the aforementioned principles [concerning patentable subject matter] as any other subject matter."). Indeed, there are numerous classes of inventions in the biotechnological arts that satisfy the utility requirement.

Take, for example, the class of interleukins expressed in human cells of the immune system. Unlike the classes of steroids or plastic-like polypropylenes in *Kirk* and *Ziegler*, all of the members of this class have practical uses well beyond "throwaway" uses. All of them cause some physiological response (in cells of the immune system). All of the genes encoding them can be used for toxicology testing to generate information useful in activities such as drug development, even in cases where little is known as to how a particular interleukin works. No additional experimentation would be required, therefore, to determine whether an interleukin has a practical use. It is well-known to persons of ordinary skill in the art that there is no such thing as a useless interleukin.

Because all of the interleukins, as a class, convey practical benefit (much like the class of DNA ligases identified in the Training Materials), there is no need to provide additional information about them. A person of ordinary skill in the art need not guess whether any given interleukin conveys a practical benefit or how that particular interleukin works.

Another example of a class that by itself conveys practical benefits is the G protein-coupled receptors ("GPCRs"). GPCRs are well-known as intracellular signaling mediators with diverse functions critical to complex organisms. They perform these functions by binding to and interacting with specific ligands. They are targets of many current drug treatments, including anti-depressants, anti-histamines, blood pressure regulators, and opiates.

Newly-identified GPCRs are used intensively in the real-world, even in cases where

neither the specific ligand that binds to the GPCR or the precise biological function of the GPCR is known. Newly identified GPCRs are used, for example, as toxicity controls for drug candidates known to bind other GPCRs. Because a person of ordinary skill in the art would know how to use any GPCR to achieve a practical benefit, even without any detailed or particular knowledge as to how it works, GPCRs as a class meet the utility requirement.

In fact, **all** isolated and purified naturally-occurring polynucleotide and polypeptide sequences which are expressible (i.e., which are not pseudogenes that are never expressed during any natural biological process) can be and **are** used in a real-world context as tools for toxicological testing, e.g., for drug discovery purposes. This utility applies to all sequences actually expressed, yet in each case, the utility of the sequence is quite specific, e.g., insofar as it is used to detect its own specific complementary sequence in a sample containing many different sequences.

Kallikreins, like interleukins, GPCRs and fishing rods is a class that by itself conveys practical benefits. Unlike steroids and "plastic-like" polypropylenes, all of the kallikreins are expressed by humans, and all of them can be used as tools for toxicology testing. The claimed invention could be used, for example to determine whether a drug candidate affects the expression of kallikreins in humans, how it does so, and to what extent. Just as there are no useless interleukins and GPCRs, there are no useless kallikreins. As these are practical, real-world uses, the application need not describe particular functionality or medical applications that would only supplement the utilities known to exist already.

C. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all

expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals and diagnostic tests.

II. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

In addition to alleging a "specific" use for the claimed subject matter, a patent applicant must present proof that the claimed subject matter is in fact useful. *Brana*, 51 F.3d at 1565-66. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The amount of evidence required to prove utility depends on the facts of each particular case. *In re Jolles*, 628 F.2d 1322, 1326, 206 USPQ 885 (CCPA 1980). "The character and amount of evidence may vary, depending on whether the alleged utility appears to accord with or to contravene established scientific principles and beliefs." *Id.* Unless there is proof of "total incapacity," or there is a "complete absence of data" to support the applicant's assertion of utility, the utility requirement is met. *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992); *Envirotech*, 730 F.2d at 762.

A patent applicant's assertion of utility in the disclosure is presumed to be true and correct. *In re Cortright*, 165 F.3d at 1356; *Brana*, 51 F.3d at 1566. If such an assertion is made, the Patent Office bears the burden in the first instance to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See Langer*, 503 F.2d at 1391-92. If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The Revised Guidelines are in agreement with this

procedure. *See* Revised Interim Guidelines at ¶ ¶ 3-4.

The issue of proof often arises in the chemical and biotechnological arts when the patentee asserts a utility for a claimed chemical compound based on its homology or similarity to another compound having a known, established utility. In such cases, the applicant can demonstrate "substantial likelihood" of utility by demonstrating a "reasonable correlation" between the utility -- not the function -- of the known compound and the compound being claimed. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895 (Fed. Cir. 1996). Accordingly, under *Brana*, the Patent Office must accept the asserted utility unless it can show that a person of ordinary skill in the art would reasonably doubt that a "reasonable correlation" exists. If the Patent Office makes such a showing, however, the applicant may submit evidence in support of the correlation.

In the present case, the specification (pages 11-12) clearly discloses that the claimed HPAK has:

> chemical and structural homology with human pancreatic kallikrein (GI 186653; SEQ ID NO:3). In particular, HPAK and human pancreatic kallikrein share 54% identity. HPAK's amino terminal 24 amino acids are hydrophilic and closely resemble signal sequences important for kallikrein secretion (Figs. 2, 3, and 4). HPAK sequence contains conserved residues critical for serine protease activity, H_{65}, D_{113}, and S_{206} (Fig. 2). Amino acid residue D_{200} is likely to confer on HPAK chymotrypsinogen-like activity. HPAK amino acid sequence includes 10 conserved cysteine residues (31, 50, 66, 145, 166, 177, 191, 202, 212, and 227; Fig. 2). In the kallikreins mentioned above, these cysteines are structurally important and form five disulfide bonds. As illustrated by Figs. 3 and 4, HPAK and human pancreatic kallikrein have rather similar hydrophobicity plots. Northern analysis reveals the expression pattern of this sequence in various libraries (Fig. 5). Of the 15 tissues in which HPAK is expressed, six are from the prostate gland and seven come from cancer patients. (See Specification, page 11, lines 8-19).

This is certainly "objective evidence" (not that any objective evidence was required) of the credibility of the utility. In further support of this assertion, Applicants direct the Examiner's attention to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a dataset of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.)

The specification illustrates that SEQ ID NO:1 and human pancreatic kallikrein protein (GI 186653, SEQ ID NO:3) share 54% identity (Figure 2), thus meeting the criteria of Brenner et al. Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.) SEQ ID NO:1 and human pancreatic kallikrein (GI 186653) also meet these criteria, as the region of SEQ ID NO:1 from M1-H110 shows ungapped identity to human pancreatic kallikrein (GI 186653) at 72 out of 110 residues, corresponding to 65% sequence identity. Therefore, SEQ ID NO:1 and human pancreatic kallikrein (GI 186653) share sequence identity that exceeds the thresholds proposed by Brenner et al. Thus, SEQ ID NO:1 is a true kallikrein homolog by these criteria. Since these criteria are based on a dataset of homologous proteins with shared structural and functional features, one of ordinary skill in the art would likewise expect SEQ ID NO:1 to possess the evolutionarily conserved structural and functional characteristics of kallikrein. Hence, the "reasonable correlation" standard as set by case law has been met.

In the present case, the Office Action purports that the degree of amino acid identity between HPAK and other kallikrein family proteins is insufficient to establish that HPAK is a member of the kallikrein family of proteins and thus shares the same utilities. The Examiner attempted to support this assertion with the teachings of Bowie et al. (Science (1990) 247:1306-1310), Lazar et al. (Mol. and Cell. Biol. (1988) 8:1247-1252), and Burgess et al. (J. Cell Biol. (1990) 111:2129-2138), all of record and addressed below. However, all of these references fail to support the outstanding rejections.

The teachings of Bowie et al. are, in part, counter to the outstanding rejections, and in part, supportive of the asserted utilities of HPAK based on amino acid sequence homology to kallikrein family proteins. Careful review of this reference reveals that the teachings of Bowie et al. are directed primarily toward studying the effects of site-directed substitution of amino acid residues in certain proteins in order to determine the relative importance of these residues to protein structure and function. As discussed below in further detail, such experiments are not relevant to Applicants' use of amino acid sequence homology to reasonably predict protein function.

In support of Applicants' use of amino acid sequence homology to reasonably predict the

utility of the claimed polypeptide, Bowie et al. teach that evaluating sets of related sequences, which are members of the same gene family, is an accepted method of identifying functionally important residues that have been conserved over the course of evolution. (Bowie et al., page 1306, 1st column, last paragraph, and 2nd column, 2nd full paragraph; page 1308, 1st column, last paragraph; page 1310, 1st column, last paragraph.) It is known in the art that natural selection acts to conserve protein function. As the Examiner stated and as taught by Bowie et al., proteins are tolerant of numerous amino acid substitutions that maintain protein function, and it is natural selection that permits these substitutions to occur. Conversely, mutations that reduce or abolish protein function are eliminated by natural selection. Based on these central tenets of molecular evolution, Applicants submit that the amino acid differences among the polypeptide encoded by Applicants' claimed polypeptide and known kallikreins are likely to occur at positions of minimal functional importance, while residues that are conserved are likely those that are important for protein function. One of ordinary skill in the art would further conclude that the level of conservation observed between Applicants' claimed polypeptide and polypeptides encoding kallikreins is indicative of a common function, and hence, common utility, among these proteins.

The Examiner further cited Lazar et al. and Burgess et al. as demonstrating that "even a single amino acid change can alter protein function . . . " (Office Action, page 4.) However, these references are not relevant to the case at hand. Lazar et al. describe the mutagenesis of two amino acid residues that are highly conserved among EGFs and TGF-αs. Similarly, Burgess et al., describes mutagenesis of HBGF-1 at an amino acid residue known to be important for ligand binding. In both of these cases, particular amino acid residues with known importance to protein function were specifically targeted for site-directed mutagenesis. These mutations were "artificially" created in the laboratory and, therefore, are **not** analogous to molecular evolution, which is profoundly influenced by natural selection. For example, the deactivating mutations as described by Lazar et al. and Burgess et al. would almost certainly not be tolerated in nature. Furthermore, it is clear that over the course of evolution, amino acid residues that are critical for protein function are **conserved**. Thus, the amino acid differences between SEQ ID NO:1 and human pancreatic kallikrein are likely to represent substitutions that do **not** alter protein function. Therefore, the teachings of Lazar et al. and Burgess et al. are not relevant to the case at hand.

The Office Action also cited Bork to support the outstanding rejection. Bork states that there are "pitfalls associated with comparative sequence analysis for predicting protein function" and that "computational sequence analysis is far from perfect." However, Bork emphases "high-throughput technologies." Human pancreatic kallikrein (GI 186653), on the other hand, was analyzed by both laboratory and computational sequence analysis, not the allegedly error-prone high-throughput technologies being denounced by Bork. Consequently, the classification of human pancreatic kallikrein as a serine protease of the kallikrein family is credible scientific evidence and further, has been substantiated by peer review, i.e., those who are skilled in the art (see Fukushima, D. et al., (1985) Biochemistry 24:8037-43, of record). Therefore, a sequence such as SEQ ID NO:1 which shares more than 50% homology with human pancreatic kallikrein (GI 186653) not only meets, but exceeds, the criteria of Brenner (*supra*).

The cited evidence is completely insufficient to support the rejections of the claims. The only relevant evidence of record shows that a person of ordinary skill in the art would not doubt that the claimed polypeptide is in fact a member of the kallikrein family of proteins, which are known to have specific utility.

By ignoring the "reasonable correlation" requirement in the case law and failing to illustrate the procedure established by *Brana*, the Examiner has failed to set forth a proper *prima facie* case, and the rejection does not shift the burden of proof to Applicants for rebuttal. In fact, the rejection must be withdrawn, as the Examiner has failed to meet PTO's burden in the first place of establishing a proper rejection. There is no proper rejection for Applicants to rebut.

III. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA

> target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular", *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000)("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible, "throw-away" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food" do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer

was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. *See supra* § II.B. Thus, the Training Materials cannot be applied consistently with the law.

IV To the extent the rejection of the patented invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be withdrawn as well.

The rejection set forth in the Office Action is based on the assertions discussed above, *i.e.,* that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reason.

Written description rejections under 35 U.S.C. § 112, first paragraph

Claims 1 and 20 have been rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

I. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1.

The Office Action has further asserted that the claims are not supported by an adequate written description because:

> Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed structure of the polypeptides encoded by the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it.
>
> . . . Support for allelic sequence, i.e., variants, is provided in the specification on page 13, lines 11-18 where . . . invention includes alleles of the genes encoding HPAK, which may result from at least one mutation in the nucleic acid sequence. . . . However, no disclosure, beyond the mere mention of allelic variants is made in the specification. (pages 7-8 of the Office Action of January 9, 2001)

However, the subject matter encompassed by the claims is either disclosed by the Specification or is conventional or well known to one skilled in the art. First note that the "variant" language of independent claim 1 recites "a polypeptide comprising . . . a naturally-

occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1."

The amino acid sequences of SEQ ID NO:1 is explicitly disclosed in the Specification. See, for example, Figure 1. One of skill in the art would know how to provide polynucleotide sequences encoding SEQ ID NO:1 as well as complements thereof. In this regard, the Specification also explicitly discloses the particular polynucleotide species of SEQ ID NO:2, which encode the amino acid sequences of SEQ ID NO:1, (see Figure 1). Similarly, one of skill in the art would recognize polypeptide variants of SEQ ID NO:1. The Specification further describes, *e.g.*, at page 11, lines 20-23, and page 4, lines 14-16, naturally-occurring polypeptide variants having at least 90% sequence identity with HPAK (*i.e.*., SEQ ID NO:1). Given SEQ ID NO:1 and SEQ ID NO:2, one skilled in the art would be able to describe polypeptide variants having at least 90% sequences identity with SEQ ID NO:1. Accordingly, the Specification provides an adequate written description of the recited polypeptide sequences.

The analysis in the Office Action is deficient in several ways. Perhaps most importantly, the Office Action has failed to provide an appropriate written description inquiry based "***on whatever is now claimed***," as directed in *Vas-Cath Inc. v. Mahurkar,* 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

A. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University*

of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of functional features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant phasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim 1 recites chemical structure to define the claimed genus:

1. An isolated polypeptide comprising . . .
b) a naturally-occurring amino acid sequence having at least 90% sequence identity to the **sequence of SEQ ID NO:1 . . .**

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polypeptides. The polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

B. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the reference by Brenner et al. *supra*. Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.)

The present application is directed, *inter alia*, to a novel human prostate-associated kallikrein proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as kallikrein proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language" of the present claims recites polypeptides encoding "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1"

(note that SEQ ID NO:1 has 253 amino acid residues). This variation is far less than that of all potential kallikrein proteins related to SEQ ID NO:1, i.e., those kallikrein proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

The case of *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) provides further support for concluding that the polypeptide genus defined by the present claims complies with the written description requirement. As discussed above, certain claims of U.S. Patent No. 4,652,525 were found invalid for failing to satisfy the written description requirement. The *Lilly* case, however, also considered U.S. Patent No. 4,431,740. While there is a discussion in *Lilly* of issues of infringement and enforceability of the claims of the '740 patent, there is no written description analysis of the claims of the '740 patent. However, there was no holding of invalidity of any claim of the '740 patent. Thus, the claims of the '740 patent are presumed to satisfy the written description of 35 U.S.C. §112. See 35 U.S.C. §282. Now consider, for example, claim 4 of the '740 patent, which reads as follows:

> 4. A DNA transfer vector comprising a deoxynucleotide sequence coding for human pre-proinsulin consisting essentially of a plus strand having the sequence:

5'-$_{-24}$ GCL$_{-23}$ X$_{-22}$ TY$_{-22}$ TGG-$_{21}$ ATG$_{-20}$ W$_{-19}$ GZ$_{-19}$ X$_{-18}$ TY$_{-18}$ X$_{-17}$ TY$_{-17}$ CCL$_{-16}$ X$_{-15}$TY$_{-15}$ X$_{-14}$ TY$_{-14}$ GCL$_{-13}$ X$_{-12}$ TY$_{-12}$ X$_{-11}$ TY$_{-11}$ GCL$_{-10}$ X$_{-9}$ TY$_{-9}$ TGG$_{-8}$ GGL$_{-7}$ CCL$_{-6}$GAK$_{-5}$ CCL$_{-4}$ GCL$_{-3}$ GCL$_{-2}$ GCL$_{-1}$ TTK$_{1}$ GTL$_{2}$ AAK$_{3}$ CAJ$_{4}$ CAK$_{5}$ X$_{6}$ TY$_{6}$ TGK$_{7}$ GGL$_{8}$ QR$_{9}$ S$_{9}$ CAK$_{10}$ X$_{11}$ TY$_{11}$ GTL$_{12}$ GAJ$_{13}$ GCL$_{14}$ X$_{15}$ TY$_{15}$ TAK$_{16}$ X$_{17}$ TY$_{17}$ GTL$_{18}$ TGK$_{19}$ GCL$_{20}$ GAJ$_{21}$ W$_{22}$ GZ$_{22}$ GCL$_{23}$ TTK$_{24}$ TTK$_{25}$ TAK$_{26}$ ACL$_{27}$ CCL$_{28}$ AAJ$_{29}$ ACL$_{30}$ W$_{31}$ GZ$_{31}$ W$_{32}$ GZ$_{32}$ GAJ$_{33}$ GCL$_{34}$ GAJ$_{35}$ GAK$_{36}$ X$_{37}$ TY$_{37}$ CAJ$_{38}$ GTL$_{39}$ GGL$_{40}$ CAJ$_{41}$ GTL$_{42}$ GAJ$_{43}$ X$_{44}$ TY$_{44}$ GGL$_{45}$ GGL$_{46}$ GGL$_{47}$ CCL$_{48}$ GGL$_{49}$ GCL$_{50}$ GGL$_{51}$ QR$_{52}$ S$_{52}$ X$_{53}$ TY$_{53}$ CAJ$_{54}$ CCL$_{55}$ X$_{56}$ TY$_{56}$ GCL$_{57}$ X$_{58}$ TY$_{58}$ GAJ$_{59}$ GGL$_{60}$ QR$_{61}$ S$_{61}$ X$_{62}$ TY$_{62}$ CAJ$_{63}$ AAJ$_{64}$ W$_{65}$ GZ$_{65}$ GGL$_{66}$ ATM$_{67}$ GTL$_{68}$ GAJ$_{69}$ CAJ$_{70}$ TGK$_{71}$ TGK$_{72}$ ACL$_{73}$ QR$_{74}$ S$_{74}$ ATM$_{75}$ TGK$_{76}$ QR$_{77}$ S$_{77}$ X$_{78}$ TY$_{78}$ TAK$_{79}$ CAJ$_{80}$ X$_{81}$ TY$_{81}$ GAJ$_{82}$ AAK$_{83}$ TAK$_{84}$ TGK$_{85}$ AAK$_{86}$ TAGACGCAGCCCGCAGGCAGCCCCCCACCCGCCGCCTCCTGCACCGAGAGAGATGG AATAAAGCCCTTGAACCA GC polyA-3'

> wherein
>
> A is deoxyadenyl,
>
> G is deoxyguanyl,
>
> C is deoxycytosyl,
>
> T is thymidyl,
>
> J is A or G;

K is T or C;

L is A, T, C, or G;

M is A, C or T;

X_n is T or C if Y_n is A or G; and C if Y_n is C or T;

Y_n is A, G, C or T if X_n is C, and A or G if X_n is T;

W_n is C or A if Z_n is G or A, and C if Z_n is C or T;

Z_n is A, G, C or T if W_n is C, and A or G if W_n is A;

QR_n is TC if S_n is A, G, C or T, and AG if S_n is T or C;

S_n is A, G, C or T if QR_n is TC, and T or C if QR_n is AG; and, script numerals, n, refer to the position in the amino acid sequence of human proinsulin, to which each triplet in the nucleotide sequence corresponds, according to the genetic code, the amino acid positions being numbered from the amino end.

Claim 4 of the '740 patent recites a DNA sequence which includes the coding region for human pre-proinsulin; in particular, the 330 nucleotide bases from codon $-GCL_{24}$ through codon AAK_{86} code for human pre-proinsulin. As can be seen from the claim language, claim 4 of the '740 patent sets forth a DNA structure with numerous variant positions. Of the 330 nucleotides in the coding region for human pre-proinsulin, 141 are potentially variant positions within the structure defined by claim 4. Thus, claim 4 of the '740 patent defines a DNA which potentially is only 57% identical (189/330 x 100% = 57%) to the single species of human pre-proinsulin actually sequenced in the '740 patent. See Example 1 and Figure 2. As discussed above, the present claims encompass naturally-occurring polypeptide variants which have at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1. Clearly, then, the genus variation of the present claims is less than that of claim 4 of the '740 patent.

C. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the

benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of January 29, 1997. Much has happened in the development of recombinant DNA technology in the 17 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:2, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polypeptide variants at the time of filing of this application.

D. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides defined by the present claims is not "highly variant," as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the above reasons, the Specification provides an adequate written description

of the claimed subject matter, and withdrawal of this rejection is therefore requested.

Enablement rejection under 35 U.S.C. § 112, first paragraph

Claims 19 and 20 have been amended to remove recitation of the term "pharmaceutical." Thus, the compositions of claims 19 and 20 are no longer specific to pharmaceutical uses and the basis for this rejection no longer exists. Withdrawal of this rejection is therefore requested.

Scope rejection under 35 U.S.C. §112, first paragraph

Claims 1 and 20 were also rejected under the first paragraph of 35 U.S.C. §112 because the Specification allegedly did not provide an enabling disclosure commensurate in scope with the claims. This rejection is traversed.

The Office Action has asserted, *inter alia*, that the Specification provides insufficient guidance for one of skill in the art to obtain polypeptides that have 90% sequence identity to SEQ ID NO:1. Note, however, that the claims recite not only that the polypeptides have at least 90% sequence identity to SEQ ID NO:1, but also have "***a naturally-occurring amino acid sequence***." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Hence, referring to problems which accompany protein structure/function analysis (see the Office Action at the paragraph bridging pages 15-16) does not properly frame the issue of the difficulty involved in obtaining the claimed polypeptides.

Given the information provided by SEQ ID NO:1 (the amino acid sequence of HPAK) and SEQ ID NO:2 (the polynucleotide sequence of HPAK), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. See, *e.g.*, page 33, lines 10-22; and Example VI at page 43. Thus, one skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:1. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature.

The Office Action has further asserted that the Specification would not enable one of skill in the art to obtain the "fragments" recited by claim 1. First, note that the recitation of "biologically active fragments" has been deleted by the present amendment; thus, this issue is moot. Furthermore, the Specification describes how to obtain immunogenic fragments of SEQ ID NO:1. See, for example, the Specification at pages 24-26, which describes methods for making antibodies to polypeptides of the present invention. In addition, see Example X at pages 44-45, which describes how to determine fragments of SEQ ID NO:1 which are immunogenic:

> HPAK that is substantially purified using PAGE electrophoresis (Sambrook, supra), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols. The amino acid sequence deduced from SEQ ID NO:2 is analyzed using DNASTAR software (DNASTAR Inc) to determine regions of high immunogenicity and a corresponding oligopolypeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions, is described by Ausubel et al. (supra), and others.
>
> Typically, the oligopeptides are 15 residues in length, synthesized using an Applied Biosystems Peptide Synthesizer Model 431A using fmoc-chemistry, and coupled to keyhole limpet hemocyanin (KLH, Sigma, St. Louis, MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS; Ausubel et al., supra). Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. The resulting antisera are tested for antipeptide activity, for example, by binding the peptide to plastic, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radioiodinated, goat anti-rabbit IgG.

Accordingly, the Specification would allow one of skill in the art to practice the full scope of what is claimed. Withdrawal of this rejection is therefore requested.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1 and 18-20 have been rejected under the second paragraph of 35 U.S.C. § 112 as being indefinite. Claim 1 has been amended to remove the term "substantially." Withdrawal of this rejection is therefore requested.

Prior art rejections

Claim 1 stands rejected under 35 U.S.C. 102(a) or 102(b) as being anticipated by Marra et al, (AA073833). This rejection is respectfully traversed.

It is believed that the rejections over the Marra et al., documents are based on a misinterpretation of the claims. That is, the recitation of "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1" means that one must make a comparison across the full length of SEQ ID NO:1.

Accession No. AA073833 describes a polynucleotide sequence which has 48% identity to SEQ ID NO:2 over the entire length of SEQ ID NO:2 (400 out of 833 nucleotides). Furthermore, AA073833 is an EST and there is no indication of an "encoded fragment." Moreover, this record does not provide an indication of an appropriate reading frame or start codon. Clearly, then, AA073833 is not pertinent to the present application. For at least the above reasons, withdrawal of the §102 rejections is requested.

In addition, a §103(a) rejection of claims 1 and 20 was applied over AA073833 in view of Johnstone and Thorpe. This rejection is traversed as well.

As explained above, the EST information provided by GenBank Accession No. AA073833 would not have guided one of skill in the art to the variants or fragments of SEQ ID NO:1 which are recited by the claims. Consequently, withdrawal of the §103 rejection is also requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650)855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108. This form is enclosed in duplicate.**

Respectfully submitted,

INCYTE GENOMICS, INC.

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph beginning at line __ of page __ has been amended as follows:

INSERT PARAGRAPH(S) HERE WITH MARKINGS SHOWING CHANGES MADE

IN THE CLAIMS:

Claims 1, 19 and 20 have been amended as follows:

1. (Twice Amended.) A [substantially] purified polypeptide comprising an amino acid sequence selected from the group consisting of

a) [an] the amino acid sequence of SEQ ID NO:1,

b) a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, and

[c) a biologically-active fragment of the amino acid sequence of SEQ ID NO:1, and]

[d]c) an [antigenically-active] immunogenic fragment of the amino acid sequence of SEQ ID NO:1.

19. (Once Amended.) A [pharmaceutical] composition comprising a polypeptide of claim 18 in conjunction with a suitable pharmaceutical carrier.

20. (Once Amended.) A [pharmaceutical] composition comprising a polypeptide of claim 1 in conjunction with a suitable pharmaceutical carrier.

--**25.** A polypeptide of claim 1 which comprises a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1.

26. A composition comprising a polypeptide of claim 25 and a suitable pharmaceutical carrier.--